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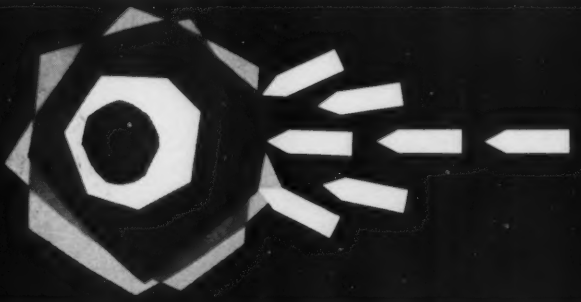

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The Adrenal Cortex During Fetal Life and Newborn Period: A Review of the Literature

H. JUERGEN WUSTROW, M.D.*

The purpose of this article is to review some of the extensive literature concerning the analysis and function of the zones of the adrenal cortex of the fetus, the premature and full term newborn, and the older infant. Two questions present themselves. The first pertains to the function of the fetal zone of the adrenal cortex, and the second to the ability of the adrenal cortex of premature and full term infants to respond to stress situations.

Embryology

The first evidence of differentiation of the future adrenal gland is observed in the 8 mm. embryo (at about 21 days of age), when coelomic epithelial cells proliferate, differentiate and migrate into the mesenchyma to form the fetal zone of the adrenal cortex.[1] The future adult cortex is also derived from the coelomic epithelium and first appears in the 11 to 13 mm. stage (at about 6 to 6½ weeks of age), overlying the previously differentiated fetal zone in the form of a cap.[2] The extension of this cap to envelop the fetal zone follows simultaneously with the invasion of the gland by chromaffin cells which differentiate into the medulla, as seen in 13 to 14 mm. embryos (at about 6 to 7 weeks of age). In the 30 to 40 mm. embryo (at about 9 weeks of age) the adrenals and kidneys are of equal size and the fetal cortex comprises nearly all of the adrenal gland. The first granules appear in the cells of the fetal cortex at this age (30 mm. embryo) and simultaneously the first basophilic cells differentiate in the anterior pituitary gland.[3]

Histology

In 1910 and 1911, four independent groups of investigators reported the presence of the so-called fetal zone of the adrenal cortex for the first time.[4-7] These authors also observed its degeneration as the permanent cortex and medulla developed, and two of them were the first to recognize the complete absence or narrowness of the fetal zone in anencephalic and hemicephalic monsters.[5, 6] Subsequently, Lewis and Pappenheimer[8] thought that the degenerative involution of the fetal zone was precipitated either by birth itself or "the altered conditions of extra-uterine life," since in both prema-

* Senior Assistant Resident, Department of Pediatrics, Georgetown University Medical Center; Formerly Resident in Pediatrics, Children's Hospital.

tures and full term newborns the fetal zones degenerated in the same way during the neonatal period. These authors eliminated sympathetic nerve transmission as the factor inducing this involution by their observation that the fetal zone of accessory adrenals without medullary tissue degenerated in a similar fashion. Newer observations by Brenner in 1940,[9] confirming those of Keene and Hewer first noted in 1927,[2] have shown that degeneration begins prior to birth in some cases. However, extensive degenerative changes generally are not observed until the fourth day of life. Evidence of rapid degeneration, demonstrated by vascular engorgement, cellular vacuolization and nuclear degeneration, is present during the second and third postnatal weeks. This is associated with proliferation of the glomerulosa and fasciculata layers of the adult cortex as well as the medulla. Eighty per cent of each adrenal degenerates during the first three weeks of life due to fetal zone involution. There is, however, only approximately a 50 per cent weight loss of the adrenal glands due to the concomitant proliferation of the other zones.[9, 10]

The fetal zone is completely atrophied by the eighth to twelfth month of life. Its only remnant is a band of fibrous tissue located between the reticularis and the medulla. This fibrous band remains throughout life. Weights and zonal measurements of adrenal glands from 311 premature and full term newborn infants, ranging in age from 1 day to 24 months, have shown similar fetal zone involution in both.[11, 12] Moeri,[13] however, has reported slower fetal zone involution in premature infants. Fetal zone development of the premature newborn may be somewhat less complete than that of the full term newborn.[9]

The question of the origin of the zona reticularis, which is located medial to the fasciculata and outside of the medulla in adult life, remains unsettled. Some authors consider its cells to have migrated down from the glomerulosa and fasciculata as maturation occurs and thus believe these cells represent exhausted cortical cells. Other investigators, however, consider it to be a distinct zone which produces androgenic hormones. Blackman[14] studied 150 adrenal glands of fetuses, infants, and older children, (hematoxylin-eosin and reticulum stained sections) and believed that the reticularis of the adult originates from persistent fetal cells lying at the periphery of the involuting fetal zone. This is in contrast to the many other observers who report complete degeneration of the fetal zone following birth.[8, 10, 11]

Hormonal Content of the Adrenal Cortex

Two zones of the adult cortex, the glomerulosa and the fasciculata, may be conveniently considered together. The active adrenal hormones of both zones are C_{21} steroids with a two carbon side chain containing an alpha-

ketol group. This side chain possesses reducing properties. Hormones produced by these two layers differ only in the extent of oxygenation at positions 11 and 17. The less oxygenated hormones, desoxycorticosterone and aldosterone,* are produced by the glomerulosa and cause sodium retention and potassium excretion (mineralocorticoids). The hormones oxygenated at positions 11, or 11 and 17, corticosterone and cortisol, are produced by the fasciculata. They increase deposition of fat, mobilize protein for gluconeogenesis, produce reduction of the total eosinophile count, shrinkage of lymphatic tissue and reversal of the urinary excretion ratio of uric acid and creatinine (glucocorticoids). Various methods for the chemical assay of corticoids are based on the reducing properties of the alpha ketol side chain and of the alpha, beta unsaturated ketone in ring A or on formaldehyde generation by oxidation of the primary alcohol group of the side chain with periodic acid. Analytic methods by paper chromatography compare speed of migration, staining properties, and characteristic ultra-violet light absorption with known corticoids for their identification. One kind of bioassay method for glucocorticoids is based on the amounts of glycogen deposited in liver tissue of adrenalectomized starving animals, while the bioassay methods for mineralocorticoids measure their influence on the serum electrolytes of test animals.

Bloch et al,[15] studied fetal adrenal extracts of three age groups: a) 9½ to 12½ weeks, b) 13 to 16½ weeks, and c) 16½ to 21 weeks gestational age. The extracts of all groups showed sodium-retaining activity by bioassay. The presence of glucocorticosteroid was detected in adrenal extracts as early as the sixteenth gestational week. These findings are in agreement with Staemmler[16, 17] who studied the corticosteroid content of adrenals from the fifth gestational month to term, using chemical separation of mineralocorticoids and glucocorticoids. He demonstrated predominance of mineralocorticoids over glucocorticoids at the fifth gestational month (ratio 1:0.73), which decreased continuously and became reversed at the time of

* Nomenclature used in this review:

1. Delta 4-pregnene-11,17,21 triol-3,20 dione; CORTISOL, Compound F, Hydrocortisone
2. Delta 4-pregnene-11,21 diol-3,18,20 dione; CORTICOSTERONE, Compound B
3. Delta 4-pregnene-11,21 diol-3,18,20 trione; ALDOSTERONE
4. Delta 4-pregnene-17,21 diol-3,20 dione; 11-DESOXYCORTISOL, Compound S
5. Delta 4-pregnene-21 ol-3,20 dione; DESOXYCORTICOSTERONE, DOC
6. Delta 4-pregnene-3,20 dione; PROGESTERONE
7. Delta 5-pregnene-3 ol-20 one; PREGNENOLONE
8. Delta 5-androstene-3 ol-17 one; DEHYDROEPIANDROSTERONE
9. Androstan-3 ol-17 one; ANDROSTERONE
10. Delta 4-androstene-3 ol-17 one; TESTOSTERONE

birth (ratio 1:1.4). He reported an average total corticosteroid concentration of 15 mcg. at the fifth lunar month which increased to 380 mcg. in the full term newborn infant. This represents a 20 fold hormonal increase, compared with only a 7 fold weight increase during the same period. Davis and Plotz[18] used C^{14} acetate as a tagged cholesterol precursor and found a high rate of cholesterol synthesis in the fetal adrenal from the third to the fifth month of intrauterine life. In contrast to these findings, an anencephalic infant's adrenal did not synthesize cholesterol to any appreciable extent. Another site of active cholesterol synthesis was in the fetal placenta but not in the maternal decidua. It is interesting that the corticosteroid content of the adrenal glands of postmature newborn infants was 10 times greater than that of full term infants.[16, 17] The glandular corticosteroid content of all infants dropped rapidly following birth, with 50 per cent reduction by the first day of life, 75 per cent by the fifth day, and 85 per cent by the twelfth day.[16, 17] Gardner and Tice[19] studied adrenal tissue extracts of 12 infants for their C_{21} corticosteroid content during the neonatal period (nine infants were less than 11 days old, one was 4 weeks, one 8 weeks, and one was premature). The pooled tissue showed only traces of corticosteroids. This finding compares well with Staemmler's observation.[16, 17]

Studies of Plasma Levels of Corticoids

Migeon[20] and Gemzell[21] demonstrated that 17-hydroxy-corticosteroid (17-OH-CS) plasma levels in pregnant women at the thirty-ninth week of pregnancy were greatly elevated over normal adult levels; there was a further tendency to rise at the time of delivery. Cord plasma levels for the same substances also proved to be somewhat higher than normal adult levels, but reached only one-fifth to one-half the maternal elevation. Davis and Plotz[16] explained this rise of maternal 17-OH-CS as caused by increased placental progesterone production, which is able to serve as an adrenal corticosteroid precursor independent of ACTH influence.

In a subsequent study, Migeon et al.[22] elevated the maternal 17-OH-CS plasma level by infusion of 25 mg. ACTH six hours prior to delivery by elective Caesarian section (range 31 to 61 mcg. per 100 ml.). In proportion the 17-OH-CS content of the umbilical cord blood rose, but remained at about one-fourth to one-half the maternal level (11.5 to 30.5 mcg. per 100 ml.). Furthermore, these investigators increased maternal 17-OH-CS plasma concentration by infusion of 50 mg. and of 100 mg. cortisol just prior to Caesarian section (range 178 to 326 mcg. per 100 ml.). Cord plasma 17-OH-CS concentration rose again proportionally to about one-fourth to one-half the maternal level (range 50 to 105 mcg. per 100 ml.). They concluded that cortisol can cross the placental barrier near the end of gestation

in a definite proportion of the maternal 17-OH-CS concentration. This suggested that at term little or no 17-OH-CS is produced either by the fetal adrenal or by the fetal side of the placenta.

Cortisol plasma levels were studied in different age groups by Klein et al.[23] Cord blood (23 determinations) showed a mean value of 17 mcg. per 100 ml.; newborn infants 2 to 5 days old (14 determinations) showed essentially no measurable cortisol (less than 0.9 mcg. per 100 ml.), one 1 week old infant had a plasma level of 13 mcg. per 100 ml., and children above the age of 3 weeks and adults showed an average of 15 mcg. per 100 ml. This corresponds with histochemical observations of Deane,[24] who studied cortical activity in fetal and prepubertal rats with the hydrazide test for carbonyl groups present in the lipid droplets of cortical cells. She found that the cells of the "inner zone" (fasciculata, ACTH dependent glucocorticoids), which were more active before birth (large cells, small droplets), had reduced secretory activity during the neonatal period (shrinkage of cells and nuclei and enlargement of droplets). During the second postnatal week these cells enlarge again and the lipid droplets become minute (return to state of activity).

The rapid reduction of plasma corticoid levels following birth and their return to normal levels during the second week of life[23, 25] may be explained in the following way: The hormones are of extrafetal origin (placental or maternal), and the rapidly decreasing blood levels are caused by loss by excretion without replacement. The greatly elevated fetal 17-OH-CS levels at the time of delivery, which are of maternal origin, have a depressing effect on the adreno-corticotropic system of the pituitary. The adrenal cortex is not stimulated to produce corticosteroids until the anterior pituitary is able to react to the low corticosteroid plasma level with secretion of ACTH. Data reviewed here favor this explanation.[22, 24]

Urinary Excretion of Corticosteroids

Studies of urinary corticosteroid excretion are difficult to interpret since many variable factors are included. These are: efficiency of renal function in the newborn period, metabolic and chemical action on the corticosteroids during their excretion and collection, and the presence of unknown intermediate corticosteroid metabolites.

Venning, Randall, and Gyorgy[26] studied the urinary glucocorticoid excretion of 12 full term and 9 premature newborn infants (four to eight weeks premature, two premature newborns of diabetic mothers) by bioassay methods. Due to low activity of the specimens, 3-day samples had to be pooled. These authors found equal urinary glucocorticoid excretion in both premature and full term infants during the first three days of life and also noted a gradual rise of corticosteroid excretion after the tenth day of life

(range 4 to 17 mcg. per 24 hours). Two prematures were studied during the acute stress-producing situation of atelectasis. They excreted much greater amounts of glucocorticoids during this period (22 and 43 mcg. per 24 hours). One of them continued to have elevated corticosteroid excretion for 50 days, although to a much lesser degree than during the period of acute stress (27 mcg. per 24 hours). Extracts from three normal human placentas contained no measurable glucocorticoids.

Read, Venning, and Ripstein[27] studied urinary 21-hydroxy-corticosteroid excretion of full term newborns by the formaldehydogenic method. A statistical comparison of the average values obtained during the first two days of life with those found during the second week showed the differences to be highly significant, with a definite trend toward increased excretion with age. The amount of corticosteroid excretion during the second week of life (0.117 to 0.582) was of the same order of magnitude as that excreted by normal adult males (0.292 to 0.49) if expressed as milligrams per square meter body surface per day. Staemmler[16, 17] investigated urinary corticosteroid excretion of full term newborn infants and also tested the urine for a pituitary-adrenal principle by means of the uropepsin test. Urinary corticosteroids were elevated on the second day of life, dropped to one-half this amount on the following day, remained at this level during the entire first week of life, and started to increase thereafter. These findings compare well with the values of the urinary uropepsin, an indicator of pituitary adrenocorticotropic activity. These are very low during the first days of life (5 units) and increase slowly during the first few weeks of life (end of first week 11.5 units, second week 45 units, third week 52 units). Zander and Solth[28] have demonstrated that the greatest amount of urinary excretion of C_{21} steroid in the full term newborn infant occurs during the first 24 hours of life. This is followed by a markedly reduced excretion which persists until the ninth day of life, after which C_{21} steroid excretion increases. This indicates an increasing excretion of 21-hydroxy-corticosteroids during the first week of life and an approach to the range of adult excretion toward the end of the second week of life. During the same time, and up to the end of the third week of life, adrenocorticotropic activity of the pituitary increases.

Lanman[29] studied the urinary excretion of formaldehydogenic steroids (or C_{21} reducing steroids) of 8 premature infants (birth weight 1000 to 2070 Gm.) during the first two months of life. No measurable changes in urinary steroids were noted during the first 10 days of life. The amounts excreted during these days when expressed per square meter body surface per day were equal to the adult excretion. A significant increase in total 24 hour excretion with age was noted over the entire period studied (up to two months). These results were confirmed by Silverman, Day, and Blodi[30]

who demonstrated that the urinary formaldehydogenic steroid excretion of prematures increased directly with body weight; these authors studied 19 premature infants aged 15 to 84 days. Cranny and Cranny[31] studied urinary excretion of 17-OH-CS in 21 premature infants (birth weight 1400 to 2500 Gm.) by the Porter-Silber chromagen method. They compared samples obtained during three age periods: first to third day of life (average 0.28 mg. per day), fourth to fourteenth day of life (average 0.65 mg. per day), and fifteenth to fortieth day of life (average 1.35 mg. per day). Values for the adult range between 2.5 to 8.0 mg. per day by this method. These authors found a highly significant relationship between the increase of excretion and age and increase of excretion and weight at the time of excretion. Chromogen excretion was not significantly related to the birth weight unless age was considered simultaneously. The authors also presented suggestive evidence that this increase in 17-OH-CS excretion is not caused by improved renal function or by augmented urinary volume. Furthermore, they demonstrated that urinary 17-ketosteroid excretion was high at birth and decreased over a period of two weeks in the full term and over a period of two to four weeks in the premature before reaching the low childhood level. This dissociation of 17-OH-CS and 17-ketosteroid excretion suggested that the portions of the adrenal cortex which produce these different corticoids behave in dissimilar fashion.

In summary, urinary excretion studies of full term newborn infants have shown increasing adrenal corticosteroid production with age following a marked reduction during the first week of life. This corresponds well with the low plasma levels during the first week of life and their subsequent rise toward adult levels, and suggests an improved adrenal cortical function after the first week of life. In the premature infant, this reduction of excretion during the first week of life was not observed. Instead, a persistent gradual increase in the amounts excreted daily was noted; adult values were approximated somewhat later than in the full term newborn infant, between the third and sixth week of life. This may indicate slower maturation of the adrenal cortical function in the premature, but two premature newborn infants are known who responded to stress situations with markedly augmented urinary excretion of glucocorticoids.

Function of the Adult-Type Cortex

The functional state of the adult zones of the adrenal cortex, the glomerulosa and the fasciculata, during the neonatal period is estimated by studying the adrenal response to the administration of exogenous ACTH or to stress. The response of the adult can be measured by the reduction of the total eosinophile and lymphocyte counts, by metabolic changes such as increased blood sugar level and an alteration of urinary uric acid/crea-

tinine ratio, and by alterations in values for serum electrolytes such as sodium and potassium.[32]

Exogenous and stress-produced ACTH cause a lipid depletion of the zona fasciculata. This is due to reduction of its cholesterol content.[33] This depletion is diffuse in children but may be focal in later life. ACTH appears to stimulate the shortening of the C_8-side chain of cholesterol to a C_2-side chain compound, delta 5 pregnenolone, the precursor substance of progesterone, which in turn is hydroxylated at positions 17, 21 and 11 to cortisol and corticosterone.

The response of total circulating eosinophiles to ACTH in the full term and the premature infant during the newborn period has been studied by several authors. Wolman[34] investigated 24 full term newborn infants and found a 50 per cent reduction of total eosinophile counts in the first 24 hours of life in two thirds of the infants in response to 5 mg. of ACTH given intramuscularly. Six of the remaining infants responded similarly to the same dose of ACTH within 48 hours after birth, and one additional infant responded satisfactorily on the third day of life. The last, a 6 pound newborn of a diabetic mother, had pretest counts of less than 5 eosinophiles per cu. mm. for the first five days of life, and responded properly on the seventh day of life. Of the 12 premature newborn infants tested, the four smallest babies (birth weight of less than 3 pounds 6 ounces) did not show the above response to 5 mg. of ACTH until the second day of life. These findings are not in agreement with a report by Klein and Hanson[35] who consider a 35 per cent reduction of eosinophile count a positive response. Upon stimulation with 0.7 to 1.0 mg. of ACTH given intramuscularly, only 3 of 45 full term newborns showed a positive response within the first 24 hours of life. Upon stimulation with 2.0 to 12.0 mg. of ACTH only 6 of 28 newborns responded positively. Seven days after birth, 0.7 to 1.0 mg. of ACTH caused an eosinopenic response in 17 of 21, and 2 mg. of ACTH in all of 4 full term newborns. The different amounts of ACTH used by these two groups of investigators make a direct comparison unfeasible. Read, Venning, and Ripstein[27] investigated only 4 full term infants and found a normal response of circulating eosinophiles to 5 to 9 mg. of ACTH in all four within the first two days of life. They measured the urinary corticoid excretion at the same time and noted that the greatest percentage reduction in eosinophiles did not always coincide with the greatest rise in urinary corticoid excretion. Three infants responded to repeated ACTH injections (5 to 9 mg. every six hours) with increased amounts of urinary corticoid excretion on the second and third day of life. However, a single dose of ACTH (largest 4.8 mg.) produced no increased urinary corticoid excretion in 5 infants studied on the seventh, ninth and tenth days of life.

An attempt to evaluate the ratio of urinary uric acid/creatinine excre-

tion in response to ACTH stimulation failed because of the wide normal variation in creatinine values and erratic uric acid excretion.[27, 34]

Klein and Rovanek[36, 37] studied serum 17-OH-CS levels and their response to exogenous and stress-produced ACTH. Twenty-six 3 day old full term infants showed average serum levels of 2.0 ± 0.67 mcg. per 100 ml. This contrasted significantly with an average value of 26 mcg. per 100 ml. (range 0 to 51 mcg. per 100 ml.) measured in forty 3 day old full term babies one hour after injection of 2.0 to 2.5 mg. of ACTH, and also with an average value of 45 mcg. per 100 ml. (range 10 to 78 mcg. per 100 ml.) in twenty 3 day old infants two hours after ACTH stimulation. Stress stimulation had similar results in twelve 1 to 5 day old infants who were studied prior to and again 2 to 24 hours after surgery. The serum 17-OH-CS levels averaged 2.0 mcg. per 100 ml. before the procedure and increased to an average of 53 mcg. per 100 ml. (range 10 to 71 mcg. per 100 ml.). Three 1 day old full term infants with intestinal obstruction had preoperative values of 0, 1.0, and 13.0 mcg. per 100 ml. and postoperative values of 55 and 100 mcg. per 100 ml. (two hours) and 24 mcg. per 100 ml. (24 hours). The authors also observed a diurnal serum 17-OH-CS pattern in newborn infants and older children with high levels occurring at 6 A.M. and low levels at 2 P.M. Control levels in adults and children as determined by these authors averaged 10 mcg. per 100 ml. with poststimulation values of 30 to 40 mcg. per 100 ml. one and two hours after stimulation. These normal values are similar to those reported by Ely et al.[25] Pooled sera of ACTH-stimulated newborn infants contained one spot with similar chromatographic migration and staining characteristics of cortisol besides other unidentified fractions. None was similar to corticosterone.[36]

Silverman et al.[30] studied the serum levels of sodium and potassium following ACTH stimulation in infants 15 to 84 days old. They found no electrolyte alterations but noticed irregular and transient hyperglycemia.

During the same year, Klein[38] investigated the alterations of urinary sodium, potassium and nitrogen in 7 premature infants (birth weight 1210 to 1800 Gm.) in response to ACTH injection. These infants were investigated when their weights had increased to between 1330 and 3125 Gm. (the oldest 41 days). Three full term newborn infants were also investigated. The sodium retention on the day of injection was negligible, but there was a significant increase in sodium excretion associated with an augmented urinary volume the following day. Larger amounts of ACTH caused increased potassium excretion on the day of injection but no change of sodium excretion until the following day, when sodium excretion and diuresis were again observed. In some cases the initial increase in potassium excretion was followed by a second increase two or three days after the ACTH stimulation. A rise in potassium excretion was always associated with an

increase in nitrogen excretion. This reaction differs from the adult response where ACTH causes sodium retention and potassium loss. No reason for this special behavior of the newborn infant, either premature or full term, is known.

All these observations present strong evidence that the majority of full term newborn infants have an adrenal cortex capable of responding like that of an adult to exogenous and stress-produced ACTH during the first days of life; this applies particularly to the glucocorticoids. The unstimulated newborn adrenal produces minimal amounts of corticosteroids. Premature infants with a birth weight of 4 pounds or more, like full term infants, respond normally by a drop of circulating eosinophiles on the first day of life. Smaller premature infants (3 pounds 6 ounces to 4 pounds) did not respond until the second day. It is interesting that three 1 day old infants responded properly to surgical stress as did two 4 to 8 week premature newborn infants under the stress situation of pulmonary atelectasis. This indicates that the pituitary adrenal system of the full term and larger premature infant is functioning properly under stress situations as early as the first day of life.

Low plasma levels of 17-OH-CS during the first week of life and the increasing trend toward adult levels by the second week of life suggest better adrenal cortical function after the first seven days of life. This correlates well with the urinary glucocorticoid excretion which is low during the first week of life and rises thereafter to reach adult-like amounts by the second week.[27] In this regard, it is interesting to review the work of Christianson and Jones,[39] whose studies showed that hypophysectomy and adrenalectomy as well as adrenalectomy alone in the pregnant rat caused definite enlargement of the adrenal glands of all members of the litter. Hypophysectomy of the pregnant rat had no influence on the weight of the fetal adrenal. The weight of the fetal pituitary gland was also increased after maternal adrenalectomy and after adrenalectomy and hypophysectomy but not changed after hypophysectomy alone. This increase in fetal adrenal and pituitary weight was not found if any accessory adrenal tissue had remained in the mother. Injection of ACTH into the completely adrenalectomized mothers caused no further fetal adrenal weight gain. Injection of ACTH into one of the fetuses of an adrenalectomized mother produced heavier adrenals in this fetus than in his litter mates. The decapitated fetus (i.e. hypophysectomized) of a litter of normal or adrenalectomized pregnant rats had similar or lower adrenal weights than his litter mates.

This work suggests that the fetal adrenal gland of rats under the governing influence of the fetal pituitary is stimulated to substitute for a deficient maternal gland. This suggests that, at least in the rat, adrenal hormones cross the placental barrier. Migeon[22] has presented evidence that, in the human, 17-OH-CS can cross the placental barrier at the end of gestation.

One may deduce that increased maternal adrenal corticoids might have a depressing action on the fetal pituitary, just as exogenous corticoids have a depressing action on the ACTH production of the anterior pituitary of the adult. We know that maternal glucocorticoids are greatly elevated prior to and at the time of delivery. This may be the reason for the low corticoid plasma level during the first week of life, coinciding with low adrenocorticotropic activity of the pituitary during this period.

The Fetal Zone of the Adrenal Cortex

It is generally believed that the innermost zone of the adrenal cortex of the newborn, the so-called fetal zone, involutes by cellular degeneration following birth. This behavior is unique for the human adrenal gland and is not found in the adrenal glands of any of the usual laboratory animals. Lanman[40] investigated many primates and mammals and was able to find a fetal zone during fetal life in leopards, in lions and in tigers (mammals); and in chimpanzees, Congo pottos, and marmoset maraquets (primates). However, the fetal zones in these animals always disappeared prior to birth. Lanman concluded that there was a transition of the cells of the fetal zone into adult cells rather than degeneration and fibrosis, as is seen in the human. In this regard, it is interesting to learn that Blackman[14] found some of the peripheral cells of the human fetal zone to persist and to become cells of the infantile reticularis. He concluded that the reticularis originated from persistent cells of the fetal zone at an early age. This report has not been confirmed and appears open for further investigation. Other authors have observed involution of the fetal zone to occur by cellular degeneration.[8, 10, 11] This involution of the fetal zone is completely normal, and occurs even if prolonged ACTH therapy is instituted as early as the second week of life.

Benirschke et al.[15, 41] studied adrenal tissue of human fetuses from the ninth to twenty-first week of gestation for its C_{19} and C_{21} steroid content by paper chromatography. They identified three androgens in the C_{19} steroid group: delta 4-androstene-3,17 dione; delta 5-androstene-3 ol-17 one; and delta 4-androstene-11 ol-3,17 dione. The C_{19} steroid concentration decreased with advancing age while the C_{21} content increased continuously from the ninth week of gestation. There was no difference between male and female fetuses. The authors see three possible explanations for this different behavior of the C_{19} and C_{21} steroids: a) an increasing C_{19} steroid release by the gland; b) reduced C_{19} steroid synthesis; and c) a greater weight increase of the gland than increase in C_{19} steroid synthesis. Swinyard's study[10] of the volume of the fetal zone showed that it reaches maximal size at the time of birth, when it is seven times as large as the adult zones of the cortex. Exogenous ACTH and stress-produced ACTH are known to produce large, fat-depleted, eosinophilic cells, which resemble cells of the fetal zone, in the fasciculata of older children and

adults. Benirschke and his group[41] therefore drew the conclusion that the fetal zone is a very active cortical zone. This favors the conclusion that the increment of C_{19} steroid synthesis is smaller than the increase in adrenal weight. The evidence of activity of the fetal zone together with evidence of increasing C_{21} steroid content of the gland with fetal age allow the conclusion that the fetal zone is producing C_{21} steroids.

Bloch, Benirschke, and Dorfman[42] were able to study the adrenal glands of a hermaphrodite with multiple congenital abnormalities who died five minutes after birth. Histologic sections showed a hyperplastic fetal zone with a large lipid content. The C_{19} steroid, delta 4-androstene-3, 17 dione, was the only steroid identified in this gland. Other authors have described the presence of hormones with androgenic properties in extracts of glands with adrenal hyperplasia.[43]

These observations do not contradict the conclusion reached above, that the fetal zone is producing C_{21} steroids. In those instances reported by Bloch et al.[42] and Jones,[43] the adrenal gland is unable to hydroxylate the C_{21} steroid precursors at positions 17, 21, or 11 to form the active hormones, cortisol, corticosterone and aldosterone. Their precursors, pregnenolone and progesterone, are therefore metabolized to C_{19} steroids which have androgenic activity. These cases are now known to result from an enzymatic defect (hydroxylases) and have a familial occurrence.

Jones[43] and Benirschke et al.[41] noted the time correlation between the peak of maternal chorionic gonadotropin levels and the largest C_{19} content of the fetal adrenal gland at about the eighth to tenth gestational week. The reduction of the C_{19} content of the fetal adrenal corresponded with the low maternal chorionic gonadotropin level reached by the thirteenth to sixteenth gestational week. Jones[44] was able to prevent involution of the x-zone of the reticularis (or fetal zone) in hypophysectomized mice by injection of gonadotropins believed to be rich in luteotropic hormone. He and other authors[40, 41] advanced the theory that the fetal zone is directly under the stimulating influence of the luteinizing effect of maternal chorionic gonadotropins during the first half of pregnancy. They believe that during the second half of pregnancy maternal estrogens act to stimulate the fetal hypothalamus, which induces the fetal anterior pituitary to produce luteinizing hormone; this in turn acts to stimulate the fetal zone of the adrenal to produce C_{19} steroids. This theory could also explain the absence of a zone resembling the fetal zone in nonprimate species, since chorionic gonadotropins are produced by the primate placenta only and are absent in other mammalian orders.

According to Migeon,[20] only two androgens (17-ketosteroids) have been thus far identified in adult plasma. These are dehydroepiandrosterone and androsterone. Several authors have demonstrated that maternal plasma

levels of dehydroepiandrosterone are diminished during the last two weeks of pregnancy in the presence of normal amounts of androsterone.[20, 45-47] Cord blood, however, has an androsterone and dehydroepiandrosterone content comparable to the plasma level of normal adults,[45, 48] and higher than the lowered maternal dehydroepiandrosterone plasma level.[20] This points towards an extramaternal origin of fetal 17-ketosteroids. The 17-ketosteroid plasma level of the full term newborn infant continues to be elevated during the first day of life[49] but decreases rapidly to reach unmeasurable quantities by the end of the first week of life.

Gardner and Walton[50] observed higher 17-ketosteroid plasma levels in 20 premature newborn infants (793 to 2097 Gm. at birth) than in full term newborn infants. Premature infants continued to show measurable plasma values for as long as six weeks postnatally. This is in accordance with a report by Moeri[13] who observed retardation of fetal zone involution in adrenal glands of premature infants. Tahka,[11] however, was unable to demonstrate any difference in the rate of involution between the fetal zone of premature and full term newborn infants.

An index of the high 17-ketosteroid plasma level of the full term newborn and its abrupt decrease during the neonatal period is the urinary 17-ketosteroid excretion. This excretion is also highest during the first day of life (an average value of 1.2 mg. per 24 hours) and diminishes during the neonatal period to reach about 0.5 mg. per 24 hours at an age of 1½ weeks.[27, 47] It remains below this level throughout the first year of life (0.23 mg. per 24 hours at 9 months, 0.22 mg. per 24 hours at 10 months). Ulstrom and Doeden[51] studied urinary 17-ketosteroid excretion in adults, preadolescents, and full term and premature newborn infants by the column fractionation method. They reported the urinary 17-ketosteroid content in three fraction groups: fraction II–III contained androsterone; fraction IV–V contained dehydroepiandrosterone, testosterone, etiocholanolone, delta 9-androstene-3 ol-17 one, and delta 9-etiocholen-3 ol-17 one; and fraction VI–VII contained 11 hydroxy 17-ketosteroid (table 1).

Fraction VI–VII (11 hydroxy 17-ketosteroid) was the largest fraction in full term infants (age 2 weeks to 10 months) and accounted for 32 to 38 per cent of the total amount. Preadolescents and adults, however, excreted the largest portion in fraction IV–V (30 to 65 per cent), and premature infants 2 to 10 weeks of age also excreted the largest portion in fraction IV–V with dehydroepiandrosterone comprising 25 to 40 per cent.[51, 52] This is in good correlation with the studies of 17-ketosteroid plasma levels by Migeon.[20]

This difference in the 17-ketosteroid excretion pattern is unexplained and its significance unknown. Urinary 17-ketosteroid excretion patterns in premature infants with a birth weight of 1800 to 2500 Gm. were similar to those of full term newborn infants: large amounts were excreted during the first

TABLE 1

Excretion of Urinary 17-ketosteroids

Age Group	Fraction II–III	Fraction IV–V	Fraction VI–VII
	per cent	*per cent*	*per cent*
1. Adults and Preadolescents	0–42	30–65	5–25
2. Full Term, 2 weeks to 10 months	3–17	8–24	32–38
3. Premature, 2 weeks to 2½ months	5–12	25–40	8–30

Fraction: II–III = Androsterone
Fraction: IV–V = Dehydroepiandrosterone, testosterone, etiocholanolone, Δ9-androstene-3α-ol-17one, Δ9-etiocholen-3α-ol-17one
Fraction: VI–VII = 11OH-17-KS

24 hours of life followed by rapidly decreasing amounts. Premature infants with a birth weight below 1700 Gm. showed the high 17-ketosteroid excretion not only during the first day of life but persistently over a prolonged period, with average amounts of 0.77 mg. per 24 hours at 6 weeks and 0.52 mg. per 24 hours at the age of 2½ months.[52] Again this is in good correlation with the persistence of measurable amounts of 17-ketosteroids in the plasma of premature infants as long as six weeks postpartum, as compared with the early diminution by the end of the first week in full term newborn infants.

The foregoing data on the glandular content of 17-ketosteroid, the plasma level, and the amount of urinary excretion seem to support two possible explanations. Gardner[53] expressed the belief that the elevated 17-ketosteroid plasma content and the augmented urinary excretion during the first 24 to 48 hours of life, followed by diminising to absent levels by the end of the first weeks, point toward an extrafetal origin of these compounds. The differences of the 17-ketosteroid fractions of the mother and the newborn infant speak strongly against this explanation. Benirschke, Bloch, and Hertig,[41] together with other investigators, however, believe that this behavior of the 17-ketosteroids during the neonatal period and early infancy supports the assumption that the fetal zone is the producer of these compounds. Since there is also presumptive evidence that the fetal zone is the site of C_{21} synthesis,[10, 15, 41] the question about the function of the fetal zone has remained unanswered.

SUMMARY AND CONCLUSIONS

1. 17-hydroxy-corticosteroids are able to cross the placental barrier at the end of gestation, resulting in adult-like cord plasma levels and increased urinary excretion during the first few days of life.

2. After the first two days of life, 17-hydroxy-corticosteroid plasma levels and urinary excretion values are negligible until the ninth to twelfth day of

life, when they increase to approach adult values by the end of the second week of life. This is supported by histologic studies.

3. Information about adrenocorticotropic activity of the pituitary during the neonatal period is scant. There is evidence of good corticosteroid response to exogenous ACTH and stress stimulation of full term and larger premature newborn infants of more than 1800 Gm. (4 pounds). This suggests that the adrenocorticotropic activity of the pituitary is reduced during the first week of life. One alternate possibility will explain these findings, i.e., corticosteroids are produced at a site other than the adrenal following exogenous ACTH and stress stimulation.

4. Premature newborn infants with birth weights of less than 1800 Gm. respond improperly to exogenous ACTH and stress stimulation during the first week of life.

5. Review of the literature in regard to the function of the fetal zone of the adrenal gland is not conclusive. It suggests that this zone is the site of production of hormones with androgenic properties. Whether this zone produces primarily C_{21} steroids that are metabolized to C_{19} steroids with androgenic activity or produces only C_{19} steroids remains unanswered.

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Anomalous Left Coronary Artery Arising from the Pulmonary Artery*

Report of a Case Diagnosed Clinically and Operated upon, with Autopsy Findings

WELLINGTON HUNG, M.D.†
BERNARD J. WALSH, M.D.‡

The first recorded case of the left coronary artery arising anomalously from the pulmonary artery was described by Abrikossoff[1] in 1911. Origin of the left coronary artery from the pulmonary artery is rare, having been found in only 1 out of 6,800 consecutive autopsies at the Massachusetts General Hospital,[2] and in 2 out of 7,800 consecutive autopsies at the Mount Sinai Hospital in New York.[3] Some authors have suggested that this anomaly is more frequent than is supposed, since some of the cases have probably been diagnosed as idiopathic cardiac hypertrophy or thymic death.[4, 5] The condition has been called the Bland-White-Garland syndrome in recognition of those who, in 1933, first gave a classical clinical description.[2] A review by Soloff,[6] in 1942, led him to conclude that the majority of patients with this anomaly presented a sufficiently characteristic clinical picture to permit antemortem diagnosis. Eidlow and Mackenzie,[7] in 1946, made the first clinical diagnosis in a living patient. Since then antemortem diagnosis has been made on several occasions, and was made for the first time at this hospital in May 1950 by one of us (B. J. W.). In 1959, Kuzman, Yuskis and Carmichael[8] noted the reports of 48 cases of anomalous origin of the left coronary artery from the pulmonary artery in infants and added 3 of their own cases. No attempt will be made in this paper to review the literature completely, since there have been several excellent reviews published.[3, 4, 9-11]

This report is concerned with an infant whose left coronary artery originated from the pulmonary artery, in whom the correct diagnosis was considered as probable prior to operation, and in whom an attempt was made to improve the abnormal physiology by surgical means. This patient was reported as having surgery performed in a previously published paper.[12] The child lived 11 months following ligation of the anomalous left coronary artery at its origin. The necropsy findings are described.

* From the Cardiac Clinic, Children's Hospital.
† Assistant Chief Resident, Children's Hospital.
‡ Attending Staff, Chief, Department of Cardiology, Children's Hospital.

CASE REPORT

K. B. R., a 4 month old Negro female infant, was admitted to Children's Hospital on October 18, 1957 with a history of sudden onset of respiratory distress accompanied by cyanosis of the lips of 2 hours' duration. Pregnancy and delivery had been normal, and the infant weighed 6 pounds at birth. Weight gain had been satisfactory.

The infant was asymptomatic until two hours prior to admission, when she developed respiratory distress and cyanosis of the lips. She was seen by a private physician and sent to the hospital.

Physical examination revealed a well developed, well nourished, cyanotic, extremely dyspneic infant. The temperature was 101.6°F. The respirations were grunting in character. The heart rate was 190 per minute, with a regular rhythm. The heart sounds were of good quality, and no murmurs were heard. There were fine rales heard throughout both lungs. The liver edge was felt 3 cm. below the right costal margin.

A roentgenogram (fig. 1) taken on admission revealed marked enlargement of the heart. The white blood cell count was 7,100 per cu. mm., with 43 per cent segmented forms, 2 per cent bands, 51 per cent lymphocytes, 2 per cent monocytes, 1 per cent basophiles, and 1 per cent eosinophiles; the hemoglobin was 8.9 Gm. per 100 ml., and the hematocrit was 27.

The electrocardiogram (fig. 2) was abnormal, with deep Q waves in Leads 1, AVL, V_5 and V_6.

Digitalis was given rapidly in full dosage, and the child was placed in an oxygen tent. Intravenous fluids were supplied, and chloromycetin monosuccinate, 140 mg., was given intravenously every six hours. On this regimen, improvement was steady, and the symptoms of congestive heart failure disappeared within three days.

Review of the findings, with particular interest in the electrocardiogram, by the members of the Cardiac Clinic Staff led to the diagnosis of probable anomalous coro

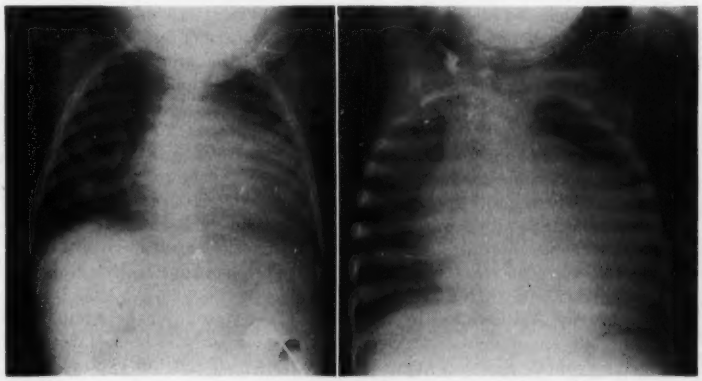

FIG. 1. The first x-ray (left) was taken October 18, 1957, and shows the cardiac size and configuration at the age of 4 months when the patient first entered the hospital. The second x-ray (right) was taken September 6, 1958 several hours before the patient expired, 11 months after ligation of the anomalous left coronary artery.

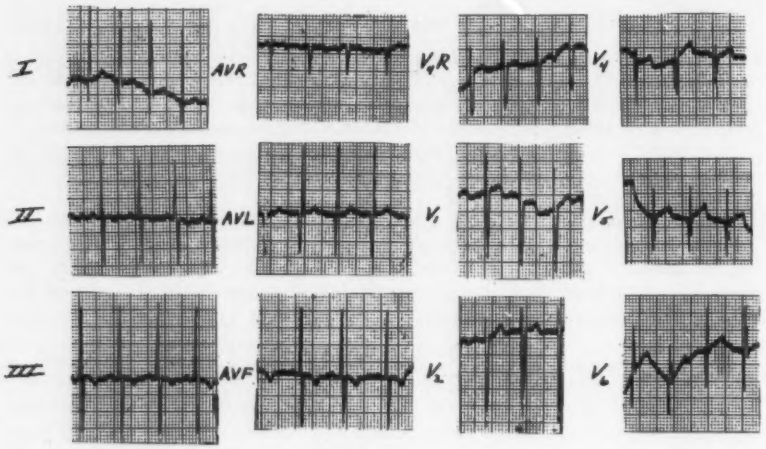

FIG. 2. Electrocardiogram taken on October 18, 1957, shortly after the child first entered Children's Hospital. There was no significant change in subsequent electrocardiograms, including those taken 11 months after ligation of the anomalous left coronary artery. Note the abnormal Q waves in Lead 1, AVL, and V_4, V_5, and V_6.

nary artery arising from the pulmonary artery. It was recommended that thoracotomy be carried out, and that if the left coronary artery was seen to arise from the pulmonary artery ligation of the coronary artery be done, as suggested by Case et al.[12]

On October 29, under general anesthesia, a left thoracotomy was performed by Dr. Edgar W. Davis and his associates. The pulmonary artery was easily visualized and at its base presented many large tortuous venous channels. In addition, the left coronary artery was seen to arise from the base of the pulmonary artery. It was doubly ligated about 2 mm. from its origin from the pulmonary artery. The infant tolerated the operation well. The postoperative course was uneventful, and she was discharged from the hospital on November 11.

The infant was seen in Cardiac Clinic on November 14 and was doing well. She was admitted to the hospital for the second time on November 22 because of rapid respirations of 12 hours duration. Early congestive heart failure was the impression on admission, and the patient was redigitalized. Subsequently there were 11 hospital admissions for recurrent episodes of upper respiratory infections, bronchitis, or bronchopneumonia. The treatment during all hospitalizations included antibiotics and the continuation of digitalis.

The patient was last seen in the Outpatient Department on September 6, 1958 because of cough, anorexia, and restlessness. Approximately 12 hours later she suddenly became cyanotic and was again rushed to the hospital, but expired en route.

AUTOPSY FINDINGS

The body was that of a Negro female infant weighing 7 Kg. and measuring 72 cm. in length. Pertinent findings included a markedly enlarged heart which measured 11.0 x 9.0 x 6.5 cm. The heart and lungs together weighed 339 Gm. The pericardium

was markedly thickened and adherent to the entire myocardium except for the free spaces on the right angle and inferior surface which were connected with the diaphragm. The operative site, measuring 5 cm. in length, was demonstrated by the presence of black silk sutures and was located on the anterior surface of the heart. The myocardium was flabby and reddish brown. The right auricle and ventricle were lined with a grayish endocardium, and the endocardium of the left auricle and ventricle was whitish gray, firm and thickened. The left ventricle measured 1.5 cm. in average thickness. The valves were examined carefully and found to be normal. The left coronary artery arose anteriorly from the pulmonary artery and was occluded at a distance of 4.8 cm. from its origin. The orifice measured 0.3 cm. in diameter. No surgical ligature was found. (It is the authors' belief that the surgical ligature slipped distally along the course of the left coronary artery from its point of application to a point 4.8 cm. from the origin of the artery). A large right coronary artery arose from the aorta and measured 0.3 cm. in diameter. The great vessels were normally connected, and there was no evidence of interventricular defect. The ductus arteriosus was not patent.

Microscopically there was myocardial hypertrophy of both ventricles. Focal intramuscular calcification was noted in the left ventricle. With Gomori acid fuchsin stain, the endocardium was noted to be thickened in the left ventricle by virtue of an increase in elastic fibers which extended into the myocardial bundles. No inflammatory changes were noted. There was a focal fibrous thickening of the epicardium in one area of the left ventricle.

The final pathological diagnoses were:

1. Congenital heart disease
    a. Endocardial fibroelastosis
    b. Status postoperative, ligation of aberrant left coronary artery
    c. Biventricular myocardial hypertrophy
    d. Adhesive pericarditis
2. Pulmonary congestion, mild
3. Acute passive congestion of the liver

DISCUSSION

The coronary arteries are first seen as outpouching endothelial buds in the wall of the aortic bulb. Later, the bulbar septum forms to separate the aorta from the pulmonary artery. Abrikossoff[1] presented two theories: 1) The coronary artery anlage arises in the wrong location in the wall of the aortic bulb, so that the normally forming septum includes the coronary artery within the pulmonary artery, or 2) the coronary artery anlage arises normally, but the bulbar septum forms in the wrong plane, and one or both coronary arteries arise within the pulmonary artery.

The clinical effects of anomalous origin of the left coronary artery are most likely due to a coronary blood flow insufficient to meet the increasing metabolic requirement of the myocardium for oxygen in a growing infant. In the fetus, perfusion pressure in a left coronary artery arising from the pulmonary artery is greater than that in the normal left coronary artery arising from the aorta. Following birth, the pressure in the pulmonary artery gradually decreases relative to the pressure in the aorta, and the

perfusion pressure in the pulmonary artery becomes minimal at approximately 2 to 3 months of age.[8] The low oxygen content of the perfusing blood of the pulmonary artery is another factor which adds to the ischemia. Kuzman et al.[8] have used these pathophysiological disturbances to explain the chronological aspects of the usual clinical picture.

The myocardial ischemia is most marked in the subendocardial region of the left ventricle and results in endocardial fibroelastosis. This, in turn, results in the obstruction of the arteriosinusoidal and arterioluminal vessels and consequent interference in blood flow;[13] this, in turn, leads to further stasis and ischemia in the subendocardial myocardium and subsequent hypertrophy and dilatation of the left ventricle.[14] The thick endocardium may also act as a mechanical factor limiting diastolic and systolic filling.[15] The ultimate result is increased residual volume and ultimate myocardial failure.[16]

It has usually been assumed that flow in the anomalous left coronary artery is from the pulmonary artery toward the myocardium, and efforts at surgical correction have been directed at increasing the perfusion pressure or the oxygen content of the blood in the pulmonary artery. Case et al.[12] have presented evidence that flow in the anomalous left coronary artery is into the pulmonary artery, and that ligation of the anomalous vessel at its origin converts the lesion into that of a single coronary artery supplying both ventricles. They have shown that the source of this retrograde blood flow is from the normal right coronary artery through extensive anastomotic channels.

The clinical picture is fairly characteristic. These infants appear normal at birth and continue so until 2 to 3 months of age. At this time signs and symptoms occur, consisting of episodes of coughing, colic, profuse perspiration, pallor, peripheral cyanosis, tachycardia and a tachypnea which may be related to feeding. There is no cyanosis except during episodes of congestive failure. Lambert and Vlad[17] believe that the symptom of colic as a diagnostic sign in this anomaly has been overstressed. The signs and symptoms are thought to resemble the anginal attacks of adults. Cardiac murmurs, thrills, and clubbing are absent. However, the heart is greatly enlarged to the left and has a forceful apical impulse. Compression of the bronchi and lungs by the enlarged heart may result in atelectasis and bronchopneumonia.

The early diagnosis of this anomaly is important from the standpoint of prognosis. The majority of infants born with an anomalous left coronary artery arising from the pulmonary artery die within the first year of life. There have been reported, however, a number of persons living to adult life with this anomaly without any symptoms of heart disease.[3, 7, 18] The diagnosis should be suspected in any young infant who appears normal at birth, but becomes irritable, pale, cyanotic, and dyspneic at 2 to 3 months of age, especially after feeding. Physical findings reveal no murmurs but

marked cardiomegaly. Radiographic examination and fluoroscopy of the chest reveal marked cardiac enlargement, primarily of the left ventricle.

The electrocardiogram provides the chief clue for recognizing this abnormality by revealing changes which are evidence of heart muscle injury. These changes consist of abnormal Q waves (and often T waves as well) in Leads 1 and AVL, and the left precordial leads. It is important to emphasize that an anomalous left coronary artery arising from the pulmonary artery is not the only cause of an electrocardiographic pattern characteristic of myocardial infarction in infancy.

The differential diagnosis includes lesions causing acyanotic cardiomegaly in infants, such as primary endocardial fibroelastosis, glycogen storage disease of the heart, idiopathic myocarditis, idiopathic myocardial hypertrophy and rhabdomyoma. Differentiation may be difficult, especially in the patient with primary endocardial fibroelastosis, but probably can be provided in most instances by radiographic visualization with opaque dye of one or both coronary arteries. Glycogen storage disease of the heart may be differentiated by demonstration of excessive glycogen deposits in striated muscle obtained by biopsy.

Various surgical procedures have been attempted in order to improve the myocardial blood flow in those with an anomalous left coronary artery. The surgical procedures proposed include: direct anastomosis of the aorta and pulmonary artery,[10] transplantation of the coronary artery either directly to the aorta or to one of its branches,[19] poudrage in an attempt to revascularize the myocardium,[20] creation of supravalvular pulmonic stenosis in order to produce an increased arterial pressure just above the pulmonary valves,[21] resection of the myocardial infarct,[19] and ligation of the anomalous left coronary artery.[12] To date none of the above surgical procedures has been successful in prolonging life beyond a few months.

SUMMARY

A case is reported of anomalous origin of the left coronary artery from the pulmonary artery in a female Negro infant. Ligation of the anomalous coronary artery was carried out with survival of the child for 11 months postoperatively. Autopsy findings are included. There is a brief review of the literature dealing with this abnormality.

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Shoes for the Normal Foot

JOHN TKACH, M.D.*

"Natural walking surfaces" such as sandy beaches and grassy plots are excellent for strengthening feet. These surfaces are apparently those for which the foot was intended. If cleanliness were not considered, normal feet without shoes would be adequate in warm weather and on natural walking surfaces. However, man created a need for protection of the feet by inhabiting areas with extreme weather, by creating lacerating debris such as glass, and by making walking surfaces hard and unyielding.

Civilization, then, makes abnormal demands on feet; the function of the shoe of the normal foot is to protect against these demands. The shoe, however, becomes the immediate environment of the foot and can itself cause injury; in fact many of the foot complaints today are attributable to faulty shoes. One survey carried out in the schools of 39 states found that almost 80 per cent of all high school children examined had some type of foot defect. More than 50 per cent of primary school children had defective feet by the time they were ten. Since 98 per cent of infants are born with normal feet, many foot defects are being created between birth and adolescence. The most universal cause is ill-fitting and improper shoes. However, shoes that fit well help feet to develop normally and healthily.

The infant who has normal feet and has not yet begun to walk has no real need for shoes; foot covering at this stage are primarily for appearance or warmth. Even in cold weather a young baby who is still wrapped in blankets needs no stockings or shoes. Bootees are of almost no use as they are forever being kicked off. Long stockings pinned to the diaper are wet by urine. In summer, shoes or stockings are needed even less. Therefore, if shoes are provided for the nonwalking infant they should be soft and loose so that muscles can contract as freely as possible and normal development can occur. A shoe which confines any foot is a threat to the normal development.

When the baby begins to creep, shoes may be needed to protect his feet from being scratched. While baby's walking is limited to his crib or to soft yielding surfaces as a carpeted floor he still does not need shoes, but shoes with soft soles and soft uppers may be provided for him. When he begins to walk more than just a little on hard surfaces such as bare floors, and especially if he is overweight, his feet need protection. The shoe must provide for shock absorption. Such is provided in the early walking shoes by the thickness of the sole and in the later shoes by the thickness of the sole and heel.

* Formerly Assistant Chief Resident, Children's Hospital.

The first walking shoe is also designed to help the baby keep his balance—to give a firm broad base on which to step. The major difference in structure from the earlier shoe is the sole, which is firm enough to remain flat transversely but flexible enough to bend easily; it can easily be bent into an arch. The sole is ¼ inch thick and gives protection to the foot but does not interfere with its freedom. Stiff-soled shoes or stiff uppers must be avoided during this period as they make walking more difficult and jeopardize normal development of the foot by hindering contractions of foot muscles. In any age group interference by the shoe with the normal position of the foot in its normal range of motion can cause foot defects. No heels are needed on the first walking shoes as the child is not yet using a heel-toe gait.

The posterior part of the upper, the part around the heel of the foot, should be perpendicular and thus help to keep the heel of the foot in a "normal" perpendicular position. In well constructed shoes, a "counter" is present; this is a reinforcement to the leather of the posterior portion of the upper which helps to maintain the shape of the shoe and thus helps to keep the heel of the foot in a "normal" position.

At the runabout stage, about 18 to 24 months, the flat flexible sole becomes inadequate, and a sturdier shoe must be provided for the heavier and more active child. The sole is less flexible and the upper is less soft in the sturdier shoe; a heel about one fourth of an inch is present. The heel is introduced at the runabout stage, because at that time the child is beginning to develop a heel-toe gait; consequently more shock absorption is needed in the heel of the shoe. This is the beginning of the shoe of childhood; subsequent shoes are of essentially the same construction with the heel slowly becoming higher: at 6 years of age the child should be wearing a heel of about one half inch. The height of the heel increases gradually to one inch.

The high shoe has certain advantages for the first few years. The high top prevents the child from kicking or pulling the shoe off and also prevents trauma to his heel. Trauma can be caused during the first few years when the child's heels are usually insufficiently developed to hold stationary an oxford type of shoe; consequently the child's heel often becomes calloused due to rubbing by the slipping low shoe. Contrary to widespread impression, the high top shoe gives no additional support to the foot.

After the child's heel is well formed at about 2 years of age, the oxford-type of shoe is ideal. Laced shoes are preferable; straps are satisfactory if they can be made sufficiently tight to keep the shoe fitting snugly.

In general, the best shoes for children have a flexible leather sole for the maximum of foot motion, supple leather uppers to keep the toes free from pressure, a firm counter to maintain shoe shape and to help keep the heel of the foot straight, and a shank (that portion of the shoe under the midfoot) strong enough to support the midfoot. The shoe for teen-agers and adults should also have the same construction as just mentioned.

How do improper shoes cause injury to the feet?

When any shoe fits properly the toes lie straight without crowding, and there is ample room for the movement of toes, circulation of blood and ventilation of feet. Crowding of the toes (with pressure on small bones and interference with circulation) causes soft corns; pressure of the toe box causes hard corns and also causes angulation of the metatarsophalangeal joints of the great and little toes which leads to bunion formation. Tight shoes can also cause calluses; interference with circulation and muscles can lead to muscle atrophy and weakness of the foot. Shoes which are too long cause the toe of the shoe to curl up. Under such circumstances, normal foot relationships are not maintained, and strain and fatigue result. Shoes which are too loose may rub and cause blisters or may slip on the feet and cause strain. Shoes which prevent adequate ventilation can cause skin maceration and subsequent fungus infection.

Improper shoes, therefore, can cause strained or weakened arches (from excessive demands on ligaments and tendons or from muscle atrophy), toe deformities (hammer toes and hallux valgus), bursitis (bunions and retrocalcaneal bursitis), and skin pathology (blisters, corns, calluses, skin maceration and fungus infections). Signs and symptoms of these various conditions include obvious deformity, local pain, local tenderness, burning sensation of the feet, leg pain and nocturnal leg cramps.

The length of a child's shoe should be enough to allow free movement of the toes. About ½ to ¾ of an inch from the longest toe to the tip of the shoe during weight-bearing gives enough room for the toes as well as space for growth. This also allows space for the foot to sustain body weight without pressure on the tips of the toes. The shoe with the rounded toe is most apt to give adequate toe space.

The width should be sufficient to give room for the foot without crowding the toes and yet fit snugly enough to keep the foot from sliding around in the shoe. The width should be determined while the child is standing with the weight on the foot, and the widest width of the shoe which does not wrinkle across the top of the metatarsophalangeal area should be chosen. This shoe will be about ¼ inch wider than the foot.

The dorsum of the shoe should be high enough to prevent pressure on the toes and instep. The ball of the shoe should fit the ball of the foot, the first metatarsal head coming at the point of rounding in of the medial aspect of the sole. The counter should be firm and should fit the back snugly so as to provide stability to the foot. It need not be tight but should not allow motion nor irritate the ankles.

To check the fit of the shoe the child is asked to stand with the weight evenly distributed on both feet. A properly fitted shoe should fit the foot trimly. There should be no large wrinkles running from one point to another. The heads of the first metatarsal bones are palpated to see if there is too

much tension of the leather at these points and to determine if the first metatarsal head is at the point of rounding in at the medial aspect of the sole. When the foot is bent the "break" of the shoe should be indicated by lines running straight across the shoe. The position of the distal ends of the first and second toe is ascertained by pressure or by making the child force the toes against the dorsum of the shoes showing where the toes end in the shoe. The shoe is examined at the heel to see if it clings properly, and the upper margin of the shoe is observed to see if there is any gapping. Frequently one foot is larger than the other, either broader or longer or both. In such a case the shoes are fitted to the larger foot. If the difference is great, which occurs only in a true deformity, the sizes may have to be broken. Poorly built shoes which fit the foot are less apt to do harm than well built shoes that do not fit. For best results, stores that specialize in children's shoes and in careful fitting should be patronized.

At home the fit of the shoe should be checked often. It should be checked with the child standing because the child's body weight causes the foot to expand and fill out more of the shoe. As soon as the toes come within one fourth of an inch of the end of the toe, longer shoes should be bought.

Babies outgrow shoes rapidly and may need a pair of new shoes about every two to three months. Parents must be warned that outgrown shoes are a frequent cause of foot troubles in children. Parents must also be warned of the danger of their children wearing hand-me-down shoes. The danger of this practice lies in two factors: The shoes may force the child's soft malleable bones into the foot shape of the previous wearer, or may cause undue strain on his feet because they do not properly fit.

Shoe care is important to foot health. Shoes which become wet should be slowly and thoroughly dried, preferably while on shoe trees. Wrinkles in the lining and curled toes can be irritating and so should be prevented. Shoe trees are valuable to maintain the shape of the shoe at all times. Using a shoe horn to put on the oxford type of shoe is also good practice. Heels should not be allowed to be worn down too far before being repaired, as excessively worn heels can cause foot strain.

Fitting shoes by x-ray machine or fluoroscope is potentially dangerous since inexpert use of these machines could result in abnormal development of a child's foot or in x-ray burns.

SUMMARY

The function of the shoe of the normal foot is to protect against the "abnormal" demands of civilization. However, the shoe becomes the immediate environment of the foot and then can itself cause injury; many of the foot complaints today are directly due to faulty shoes.

In any age group, interference by the shoe with the normal position of the foot or its normal range of motion can cause foot defects.

For good foot care shoes should be well constructed, well fitted when obtained and discarded as soon as they become too small.

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The Editor's Column

THE PEDIATRICIAN'S ROLE IN THE RECOGNITION OF CANCER IN CHILDREN

The pediatrician's role in childhood cancer is a unique and most important one. This role must be protean: he must be a detective, a well read, informed, unbiased diagnostician, and a friend and counselor. Since the characteristics of childhood cancer include rapid growth and early metastases, and since a cure is frequently related to early diagnosis and treatment, the pediatrician who sees his patients relatively frequently is therefore in an excellent position to first suspect the diagnosis early, seek confirmation of his suspicions, and then arrange for adequate treatment. In his daily practice the pediatrician must be constantly on the alert for those clues which indicate that a malignancy may be present. He will be unable to do this, however, unless he is familiar with these clues and makes a conscious effort to look for them.

Fever, not infrequently, is the first manifestation of a malignant process in a child. This is true particularly if there is no apparent explanation for the fever, the so-called "fever of undetermined origin." Fever is an almost constant finding in the child with acute leukemia. Fever may also be a sign of a lymphoma. In the infant or child with a neuroblastoma, fever may be the initial symptom, and may occur even in the absence of a palpable intra-abdominal mass.

Pallor is another warning sign. Parents and members of the family who see the child daily may overlook this finding until the pallor has become quite obvious. On the other hand, the physician is in a position to note an early change in skin color. This should be followed by a hematological examination, and if an anemia is discovered, its cause should be accurately determined. *No anemia should be treated unless a good peripheral blood smear has been examined by a competent hematologist.*

Another clue is leg pain. There are many etiologies for this complaint in children. The careful pediatrician will not pass this symptom over lightly. He will not offer such explanations as "growing pains" or "too much exertion." This complaint is not unusual in acute leukemia, and it is encountered also in neuroblastoma.

The symptoms of pallor, fever and leg pain are a common early triad in leukemia. If we were to add to this triad a history of easy bruising, the clinical features of acute leukemia as it is manifested in childhood would be almost complete.

Malignant tumors in children grow rapidly and metastasize early. A large mass may appear in the abdomen in an amazingly short period of time—from one office visit to the next. It is not necessary to dwell on the significance of an intra-abdominal mass in a child; no other symptom need be present. Frequently it is these tumors where "cure" is closely equated with "early diagnosis." Therefore, a careful and complete examination must be performed, and the abdomen of the child should be painstakingly and gently palpated on every visit to the physician's office.

The physician should be wary of the infant whose mother exclaims proudly, "My baby has such large, beautiful eyes." Such an infant may have glaucoma and a retinoblastoma. A disturbance in gait is often the earliest sign of an intracranial neoplasm. Vomiting, which accompanies so many diseases in children, unfortunately is a common early sign of a brain tumor. In these infants and children, the funduscopic examination may be rewarding and should not be neglected. Dull pain localized to a knee with associated soft tissue swelling in an older child may herald the presence of an osteogenic sarcoma. Wartlike growths in the perineal area are often associated with rhabdomyosarcomas.

The pediatrician's role does not end with detection and diagnosis. On his shoulders falls the responsibility of following through. He should be well versed in the more recent advances in the treatment of childhood can-

cer. He should be aware of the available diagnostic and therapeutic facilities in his community, and he must make every possible effort to secure these facilities for his patient. In this regard, his choice of consultants is of paramount importance. His selection should not be dictated out of friendship or school ties, but in the best interests of the child. He should seek the services of the most experienced hematologist, pathologist, radiologist, or surgeon in the particular field. In most of these situations, the consultant is a stranger to the patient and the patient's family. The role of "liaison officer" falls to the pediatrician. His familiar presence is not only desirable but also necessary for the welfare of his patient.

The pediatrician should be familiar with research programs in cancer which are underway in his community. If his patient's problem lends itself to one of these programs, another of his responsibilities is to influence the family to participate in such programs. Not too infrequently, he must also play the role of an economic advisor. He will usually be familiar with the financial status of the family, and since cancer is often an expensive proposition, he may have to advise the family in this respect.

The pediatrician must be a friend and counselor, both to the child and the child's family. It is his responsibility to notify the family of the diagnosis, the plan of treatment and the prognosis. His tact and gentleness will help immeasurably in gaining acceptance of the facts and in assuring for his patient the best care and easiest possible course under the circumstances. The hospital stay of such a child is often a painful and prolonged experience. Too frequently, the ultimate outcome is a relatively hopeless one. As friend and counselor, he can make the situation more tolerable.

In this disease, perhaps more than in any other, the pediatrician must be the complete physician. The pediatrician who cares for a child with cancer should strive to be to his patient and the patient's family as once was described of Sir William Osler:[1]

> To have been his patient was to have obtained an almost impossible ideal of what a physician could be. In a room full of discordant elements, he entered and saw only his patient and his patient's greatest need, and instantly the atmosphere was charged with kindly vitality, everyone felt that the situation was under control, and all were attention. With his patients he recognized at once the thing or characteristic that concerned him and them; and for the rest, whatever was uncongenial or unattractive he put from his mind and prevented any expression of it. He was as merciful as he was masterful, and from the very poor and the genuinely afflicted he would even have borne being bored. Such telling love, such perfect confidence were given him that he could do what he liked without causing offense.

J. M. L.

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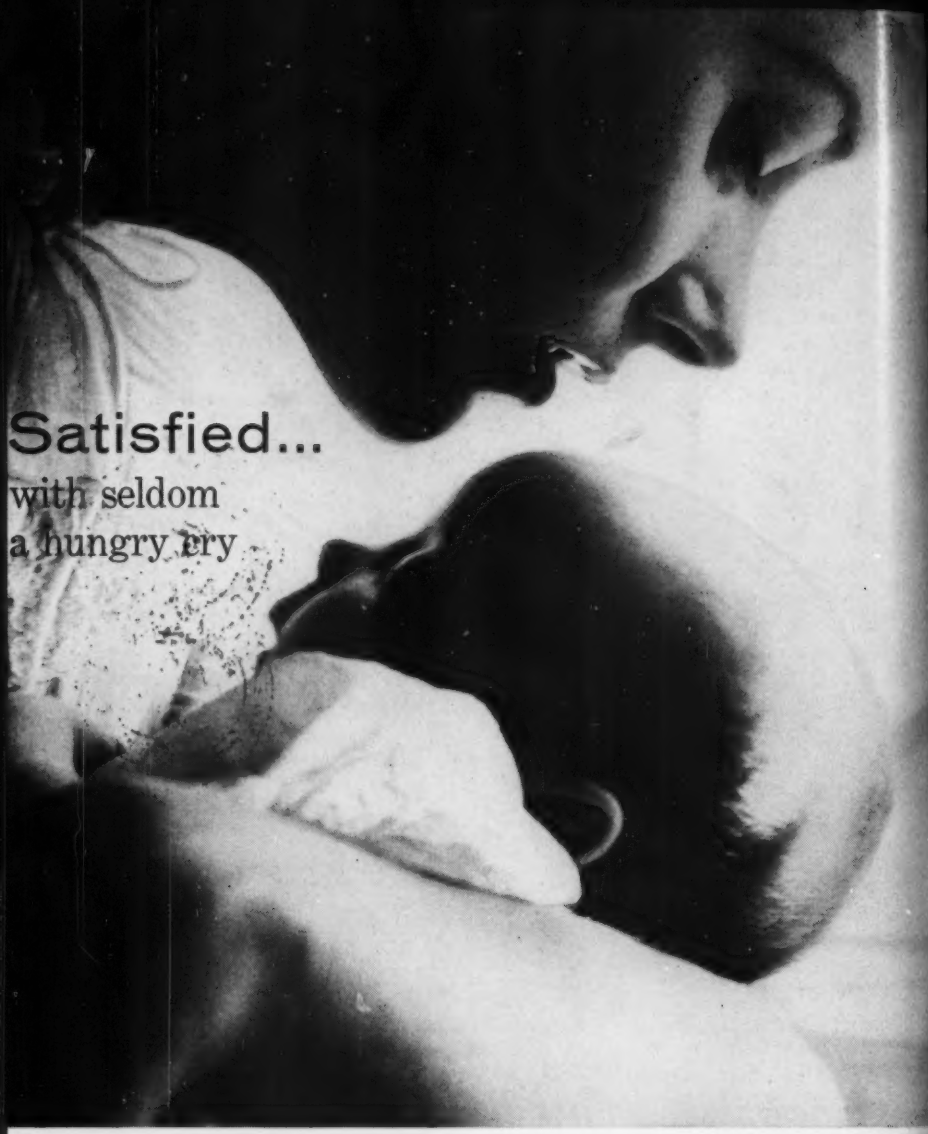

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